REMARKS

In response to the Office Action mailed April 2, 2003, Applicants respectfully request reconsideration of the above-identified application in view of the amendments and remarks presented herein.

Claims 1, 2, 7, 8, 9, 23-24 and 29-30 have been amended herein. Support for the amendments can be found generally throughout the disclosure as well as specifically as follows: support for the amendments reciting a variant sequence between 1 and 50 amino acids can be found, *inter alia*, on page 15, lines 10-11; support for the amendments reciting that the catalytic activity be at least 1% can be found, *inter alia*, on page 37, line 17 et seq. Claims 12 and 22 have been canceled. Claims 1-11, 13-18 and 23-34 are pending after entry of this amendment.

Claim 22 was rejected under 37 CFR 1.75(c), because it recites the same subject matter as claim 1. Applicants have canceled claim 22, and accordingly, this rejection is deemed moot.

Claims 1-11, 14-18 and 22-34 were rejected under 35 USC 112, second paragraph. According to the Office Action, the term "variant sequences" renders the claims indefinite. Specifically, the Office Action provided that the claims, before amendment, could be any size. These rejections are traversed based upon the amendments to the claims. Applicants have amended the claims to recite that the variant sequence is between 1 and 50 amino acids. Accordingly, reconsideration and withdrawal of the rejections are herein respectfully requested.

Claims 1-18 and 22-34 were rejected under 35 USC 112, second paragraph, as being indefinite. According to the Office Action, it is unclear whether the targeting site is one or any one of (i) a mutation of specific residues in the pretargeted enzyme (ii) insertion of a stretch of amino acids comprising around 25 residues into the pretargeted enzyme, or (iii) addition of more than residues to the pretargeted enzyme resulting in the formation of a fusion protein. These rejections are believed moot based upon the amendments presented herein. Accordingly, reconsideration and withdrawal of the rejections are respectfully requested based upon the amendment.

Claim 9 was rejected under 35 USC 112, second paragraph, as being indefinite. Claim 9 has been amended to overcome the rejections and particularly point out and

distinctly claim that which the Applicants regard as the invention. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-18 and 22-34 were rejected under 35 USC 112, first paragraph, for lack of enablement. According to the Office Action, the specification, while enabling for beta-lactamase with a target site for streptavidin in the B-loop, does not provide enablement for any enzyme and any targeting site in the pretargeted enzyme. Further, according to the Office Action, the specification is not enabling for a targeted enzyme wherein the targeting site has two or more variant sequences. Additionally, the Office Action recites that the specification is not broad enough to provide for enablement where the targeted enzyme is any enzyme activity. Finally, the Office Action recites that the specification is not broad enough to provide enablement where the targeted enzyme comprises the activity of a protease, carboxypeptidase, etc., as recited in claim 17. These rejections, and each of the objections articulated herein as well as in the Office Action, are believed moot in view of the amendments presented herein. Accordingly, reconsideration and withdrawal of the rejections are respectfully requested.

Claims 1-18 and 22-34 were rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the invention was filed, had possession of the claimed invention. Specifically, according to the Office Action, the specification teaches how to make only a single representative species of the targeted enzyme and does not teach the structure of the representative species. Also, according to the Office Action, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being a targeted enzyme. These rejections, and each of the objections articulated above and in the Office Action, are believed moot in view of the amendments presented herein. Accordingly, reconsideration and withdrawal of the rejections are respectfully requested.

Claims 1, 12, 14, 16, 17 and 22 were rejected under 35 USC 102(b) as being anticipated by Nakanishi et al. These rejections are traversed based upon the claims, as amended.

The Office Action does not set forth a *prima facie* case of anticipation with respect to the amended claims. A claim is anticipated only if each and every element of the claim is described in a single prior art reference (see, for example, Verdegaal Bros. v. Union Oil Co.

of California 814 F.2d 628 (Fed.Cir.1987) and MPEP 2131 et seq). Nakanishi et al. teach a targeted carbonyl reductase enzyme whereir there is a $T^{38}D$ substitution in the reductase. As amended, the present claims recite that "...the catalytic activity of the targeted enzyme is greater than at least 1% of the pre-targeted enzyme..."[1] Nakanishi et al do not teach a catalytic activity greater than 1% (e.g., the catalytic activity *kcat/Km* of the T38D mutant ("targeted" enzyme) is decreased by two-orders of magnitude with the cognate, that is, naturally occurring, cofactor NADPH and over 3-orders of magnitude for NADP as a cofactor (*see*, Table 1)). Accordingly, Nakahashi do et al not provide a *prima facie* case of anticipation with respect to the claimed invention, and reconsideration and withdrawal of the rejections are herein respectfully requested.

Claims 1-3, 5-7, 9-17 and 22 were rejected under 35 USC 102(b) as being anticipated by Maier et al. The rejections are herein traversed based upon the amended claims. Maier et al do not present a *prima facie* case of anticipation with respect to the amended claims. Maier et al. teach a targeted reverse transcriptase, wherein the transcriptase is targeted at the N-terminus with glutathione reductase and at the C-terminus with a 6X His-tag. As amended, the present claims provide that the variant sequence comprises a loop. Maier et al. do not provide that the variant sequence provide a loop Similarly, the present claims provide a variant sequence not known to bind the target independent of the targeted enzyme. Maier et al do not disclose a variant sequence not known to bind the target independent of the targeted enzyme. Accordingly, Maier et al do not provide a *prima facie* case of anticipation with respect to the amended claims, and reconsideration and withdrawal of the rejections are respectfully requested.

Claims 1, 15, 16, 17, 18 and 22 were rejected under 35 USC 102(b) as being anticipated by Vrudhula et al or Meyer et al. The rejections are herein traversed based upon the amended claims. Vrudhula et al teach an enzymatically active conjugate wherein beta-lactamase is fused to a monoclonal antibody directed to antigens present on tumour cell surfaces. Meyer et al teach an enzymatically active conjugate wherein beta-lactamase is fused to a FAB fragment directed against carcinoembryonic antigen (Table 1). As claimed, the present invention provides that the variant sequence is between 1 and 50 amino acids.

[1] Catalytic activity is generally defined by the second-order rate constant *kcat/Km* corresponding to catalysis of a biochemical reaction under physiological conditions of low substrate concentration (*see*, for example, Jencks, (1387) Catalysis in Chemistry and Enzymology, pp 615-806)

Neither Vrudhula et al nor Meyer et al teach a variant sequence between 1 and 50 amino acids. Likewise, the present claims, as amended, provide that the variant-tolerant sequence comprises a loop. Neither Vrudhula nor Meyer teach that the variant-tolerant sequence comprises a loop. Finally, the present claims provide that the variant sequence was not known to bind to the target independent of the targeted enzyme. Each of Vrudhula et al and Meyer at al teach a sequence that was known to bind to the target independent of the targeted enzyme. Accordingly, neither Vrudhula nor Meyer et al provide a *prima facie* case of anticipation and reconsideration and withdrawal of the rejections are herein respectfully requested.

Claims 23-35, 31 and 33 were rejected under 35 USC 103(a) as being unpatentable over Verdet et al in view of Maier et al, Vrudhula et al or Meyer et al and further in view of Barthelemy et al. These rejections are herein traversed based upon the amendments to the claims.

The above-cited references do not provide a *prima facie* case of obviousness with respect to the amended claims. To establish a *prima facie* case of obviousness, all claim limitations must be taught or suggested by the references alone or combined (*see*, for example, MPEP 2143 et seq). The cited references, alone or together, do not teach or suggest each and every limitation, as provided in the amended claims, for the reasons provided above, among others. Accordingly, reconsideration and withdrawal of the rejections are respectfully requested.

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance and issuance of a formal Notice of Allowance is respectfully requested. Examiner Swope is invited to contact Applicants at (650) 846-7544 if there are additional questions/concerns.

Respectfully submitted,

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